of adduct structures. Because this strategy uses CNL scans first to identify all nucleoside adducts, and then daughter ion scans for structure elucidation, it should have great potential for application to unknown adducts and mixtures at the picomole level.

The PI will be delivering the presentation, "Development of Fast Atom Bombardment Mass Spectral Methods for the Identification of Unknown Carcinogen-nucleoside Adducts," at the International Agency for Research on Cancer Conference, which is jointly sponsored by the National Center for Toxicological Research, October 26 - November 1, 1991, in Kailua-Kona, Hawaii. In addition, the manuscript has been submitted to the Journal of the American Society for Mass Spectrometry.

JANUARY, 1992

Recent efforts have centered around improving the detection limit sufficiently (low femtomole range) that the FAB/MS method could be used in human dosimetry. The PI has investigated the use of single reaction monitoring (SRM) for the analysis of specific carcinogens (i.e., one analyte per analysis). Another MS approach, namely laser desorption/time of flight (LD/TOF) MS was also used to investigate the possibility of obtaining full scan spectra, for the analysis of unknown or multiple adducts, with femtomole sensitivity. This technique has great potential for this application because spectra are obtained based on the integration of the total signal level over time, rather than the exclusion of signal by mass filter.

The PI has demonstrated that the methods developed can be applied to in vivo samples, provided the levels of DNA modification are sufficient to allow sample sizes within their sensitivity limits to be obtained. Interferences from the biological matrix were not noted in this experiment, suggesting that the major emphasis of the future work should be directed towards continued improvements in the sensitivity.

In addition, the PI is attempting to sort out the fragmentation mechanisms giving rise to the daughter ions that were previously used for structure elucidation. The use of SRM for adduct analysis is critically dependent on the selection of the correct ion (fragmentation pathway) for adduct characterization. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Femtomole Screening and Quantification Strategies for Arylamine-modified Nucleosides by FAB/MS/MS," M.P. Chiarelli, M.S. Bryant, and J.O. Lay Jr., Analytical Biochemistry, submitted.

2. "Detection and Characterization of DNA Adducts at the Femtomole Level by Desorption Ionization Mass Spectrometry," J.O. Lay Jr., M.P. Chiarelli, and M.S. Bryant, Environmental Health Perspectives, in press.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

3. "Development of Fast Atom Bombardment Mass Spectral Methods for the Identification of Carcinogen-nucleoside Adducts," M.S. Bryant, M.P. Chiarelli, and J.O. Lay Jr., Journal of the American Society for Mass Spectrometry, in press.

SEPTEMBER, 1992

A four month no-cost extension was requested to accommodate bringing in a visiting professor to the project. Dr. Paula S. Branco will contribute to the synthesis of model compounds and the isolation of modified nucleosides from tissue DNA. She and a research assistant (an MS candidate currently enrolled at UALR in the Dept. of Electronics and Instrumentation) will assume the salary monies formerly appropriated for Dr. Chiarelli, whose salary will now come from a Veterans Administration fellowship.

The PI has worked to lower the detection limit, to the low femtomole range, so that MS analysis of modified nucleosides could be applied to applications such as human dosimetry. Two independent approaches were investigated. Experiments were undertaken to determine if single reaction monitoring (SRM) had sufficient sensitivity to be applied to analyses of specific (i.e., targeted) carcinogens. This procedure is analygous to the Constant Neutral Loss (CNL) method developed during the first year of the study, except that one modified nucleoside is measured in each experiment, albeit with much improved sensitivity compared to CNL scans. In addition, he has conducted experiments using laser desorption (LD) time-of-flight (TOF) MS, a technique potentially suitable for use in applications involving unknown adducts where SRM experiments would not be feasible.

In summary, the minimum amount of nucleoside-carcinogen adduct necessary for detection of the protonated molecule and BH_2^+ fragment ion in full-scans using TMS derivatization and FAB/MS was about 1 ng. In FAB/CNL and SRM experiments the detection limits were 500 and 10 (median value) pg, respectively. The lowest detection limit observed in fulll scans was obtained using LD with a TOF instrument. Although only a small portion of the target was irradiated, spectra were observed when samples as small as 10 pg were applied to the target. For adduct levels of 1 in 10^8 nucleosides, a detection limit of 10 pg (20 femtomoles) would make the analysis of tissue samples as small as 1 gram feasible, assuming quantitative recovery in the preliminary isolation steps. Project is on schedule, considering four month extension.

Because of the recognition the PI has gained in the course of these studies, he was asked and did submit a review article covering the mass spectrometry of DNA adducts to Mass Spectrometry Reviews.

Associated Mauuscripts and Abstracts/Presentations

Issued :
"Development of Fast Atom Bombardment Mass Spectral Methods for the Identification of Carcinogen-nucleoside Adducts," Journal of the American Society for Mass Spectrometry, 3, 360-371 (1992).

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

MARCH, 1993

In the analysis of a targeted nucleoside isolated from human DNA, the human tissue sample sizes routinely available allow only 100 ug of DNA to be isolated. Until human tissue samples having higher levels of 4-ABP modification (greater than 1 adduct per 10^7) are identified, or the detection limit is lowered, experiments involving human dosimetry based on 4-ABP-nucleoside analysis are not feasible. The PI is investigating the analysis of smaller quantities of adducts, using LD/TOF MS, in an attempt to reach the "1 in 10^8" level of modification. Until then, experiments using frozen samples of dog tissue, archived at NCTR, containing known quantities of 4-ABP are being conducted.

The PI has not made any significant progress toward the analysis of DNA adducts from coal-tar dosed animals. This is a reflection of the fact that the DNA adduct levels observed in ongoing NCTR experiments for EPRI, which were to be the source of the unknown adducts, have resulted in three orders of magnitude lower levels of DNA modification than were expected.

Work continues on the refinement of the method to increase the sensitivity, specificity and the scope of application of LD/TOF for the analysis of ultra low (less than 1 femtomole) quantities of DNA adducts.

The syntheses of a number of model diol-epoxide adducts associated with human exposure to PAHs have been completed. Sufficient quantities of material have been isolated to begin analysis using FAB, MS/MS and LD/TOF mass spectrometry. Preliminary evidence indicates that the FAB mass spectral behavior of these compounds is quite different than that observed previously with arylamines.

Recent tandem MS results on acetylated and non-acetylated adducts have provided important insights into the mechanisms of fragmentation and, hence, the structure of acetylated and non-acetylated arylamine adducts.

Associated Manuscripts and Abstracts/Presentations

1. Fu, P.P., Miller, D.W., von Tungeln, L.S., Bryant, M.S., Lay Jr., J.O., Huang, K., Jones, L. and Evans, F.E. (1991) Carcinogenesis 12, 609-616.

2. Lay Jr., J.O., Chiarelli, M.P., Bryant, M.S. and Nelson, R.W. (1993) Environ. Health Perspect. 99, 191-193.

3. Chiarelli, M.P., and Lay Jr., J.O. (1992) Mass Spectrom. Rev. 11, 447-493.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

The Pulmonary Effects of ETS Exposure on Asthmatic Subjects
PI: Samuel B. Lehrer, Ph.D.
Tulane University Medical Center

The researchers will characterize pulmonary reactions to ETS and analyze the underlying mechanisms of this response. "Smoke-sensitive" and "smoke-tolerant" asthmatics as well as normal individuals will be studied to assess the specificity of ETS induced lung function changes.

Contract No.	89-0	90-11	90-11A	90-11B	90-11C
Contract Execution Date	3/17/89	4/27/90	3/8/91	3/1/92	3/1/93
Contract End Date	2/28/90	2/28/91	2/29/92	2/28/93	2/28/94
No Cost Extension					
Budget	$301,582	$270,720	$311,701	$273,561	$265,116
Budget Amendment					
Five month report due	8/91				8/93
Five month report rec'd	8/26/91				
Site visit (anticipated)					
Site visit (conducted)	8/3/89	1/11/91	1/17/92		
Report due	1/90	1/91	1/92	1/93	3/94
Report received	2/90	1/91	3/92		
Continuation approved	3/90	4/91	3/92	3/93	

STATUS: August 1991

Project is on schedule. Exposure chamber has been modified for production of gas phase smoke by HEPA filtration of sidestream smoke. Forty challenge subjects have been contacted. Thirteen have been challenged with SS-ETS. Challenge studies will continue until at least 10 reactors are identified. Reactors will be rechallenged with filtered SS-ETS. Nasal secretions will be measured by nasal lavage procedure as an extension of current study. PI is attempting to detect tobacco-specific antibody responses with immunoblotting techniques.

Co-investigator, Dr. Prem Menon, has opened a private allergy practice and is now working on this project part-time. Dr. Manuel Lopez, Chief of the Section of Allergy and Clinical Immunology at Tulane, and Dr. Jonathan Musmand have replaced Dr. Menon on this study.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

STATUS: January 1992

Fifty additional subjects have been challenged. Status update pending CIAR's receipt of continuation application.

STATUS: September 1992

Flourescent particulate matter (FPM) and UVPM for ETS monitoring were compared in the challenge chamber with the gravimetric method as reference. The FPM method offers greater sensitivity than the UVPM method with detection limits of 0.13 and 1.7 ug ETS per mL methanol for FPM and UVPM, respectively.

ETS Challenge:

Pulmonary Function Changes - 12 of 50 asthmatics challenged with ETS (1400 ug/m^3 TSP) were responders (drop in FEV_1 was greater than 20%). Three of these 12 had positive sham challenges and were dropped from the study. Seven responders can proceed in challenge studies as of March. Report of results of these alleged challenges is overdue.

Tobacco-specific antibody responses - 30 of the 50 subjects were skin tested with common aeroallergens, smoke extract, and two tobacco leaf extracts. Neither atopy nor skin test reactivity to any smoke or tobacco extract was significantly associated with reactivity to SS-ETS on challenge. IgE antibody responses to tobacco leaf extract were investigated by probing extract proteins with sera from SS exposed reactors and non-reactors. In one study, only one serum had weak IgE binding. In another study, strong IgE binding was detected in sera from both reactor and non-reactor groups. Combined results of antibody studies do not support an IgE-mediated response to ETS having a significant role in induced asthma.

Mediator levels - Studies of mediator levels in lavage fluids to determine the nasal and pulmonary response to the ETS challenge have begun in collaboration with the Laboratory of Clinical Investigation, Allergic Disease Section, NIAID, NIH.

STATUS: March 1993

Pulmonary function changes: About 10% of smoke-sensitive asthmatics actually demonstrated changes in pulmonary function from high level ETS exposure. The responses were not related to IgE antibody reactivity to tobacco allergens.

FPM as a marker for ETS: The FPM technique was evaluated in two private offices and in a private home. ETS levels were near the limit of detection for the UVPM method, but were an order of magnitude greater than the limit of detection for the FPM technique.

Skin test studies: Of the SS-ETS reactors tested, 6/10 did not react to any tobacco leaf or smoke extract; of the 4 skin test reactors, 2 responded to 1R4F leaf extract, 3 reacted to tobacco mix extract, and 2 to tobacco smoke extract. Results of these studies strongly support earlier observations that no basis exists for an allergic IgE-mediated asthmatic response to tobacco smoke.

Nasal lavage analysis after acute ETS exposure: Neuropeptide levels were found to be significantly affected by acute ETS exposure. The changes found in neuropeptide secretion could, in part, explain observed acute respiratory tract responses to ETS exposure.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Gas-phase SS-ETS challenges: Results demonstrate that most SS-ETS reactors have a positive challenge response upon gas phase exposure. This study suggests that the gas phase components in SS-ETS may be affecting an irritant response.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Lehrer S

Publications, Abstracts, and Presentations supported by CIAR

1. Menon PK, RP Stankus, RJ Rando, JE Salvaggio, and SB Lehrer. 1991. Asthmatic response to passive cigarette smoke; persistence of reactivity and effect of medications. J Allergy Clin Immunol. 88:861.

2. Menon PK, RJ Rando, RP Stankus, JE Salvaggio, and SB Lehrer. 1992. Passive cigarette smoke challenge studies: Increase in bronchial hyperreactivity. J Allergy Clin Immunol. 89:560-566.

3. Rando RJ, HG Poovey, PK Menon, and SB Lehrer. Assessment of multiple markers of ETS in controlled steady-state atmospheres in a dynamic test chamber. Amer Indust Hyg Assn J. Submitted.

4. Menon PK, RJ Rando, H Poovey, JE Salvaggio, and SB Lehrer. Provocative inhalation challenge of asthmatic subjects with sidestream cigarette smoke in a dynamic test chamber. In prep.

5. Rando RJ, KT Abera, HG Poovey, and SB Lehrer. 1992. Evaluation of fluorescent particulate matter as a specific and sensitive marker of ETS. Abstract. Presented at American Industrial Hygiene Conference and Exposition, Boston, June.

6. Menon PK, RJ Rando, and SB Lehrer. 1991. Skin reactivity to tobacco leaf (TLE) and smoke extracts (TSE) in relationship to clinical tobacco smoke reactivity. Proceedings of the American Academy of Pediatrics, New Orleans.

7. Rando RJ, PK Menon, HG Poovey and SB Lehrer. 1992. Assessment of multiple markers of ETS in controlled steady-state atmospheres in a dynamic test chamber. American Industrial Hygiene Association Journal. 53:699-704.

8. Rando RJ, HG Poovey and SB Lehrer. Use of suspended fluorescent particulate matter as a marker to ETS in air. In prep.

9. Menon PK, R Rando, H Poovey and SB Lehrer. 1992. Extra pulmonary responses to sidestream ETS during ETS provocation inhalation challenges. Proceedings of the American Academy of Pediatrics.

10. Musmand JJ, M McCants, M Lopez, P Menon and SB Lehrer. Tobacco smoke allergy: A fallacy? Ann Allergy. In press.

11. Musmand JJ, M White, M Lopez, MA Kaliner and SB Lehrer. The nasal response to ETS. J Allergy Clin Immunol. In press.

12. Lehrer SB, JJ Musmand, RJ Rando, M Lopez and M McCants. 1993. Specificity of asthmatic responses to sidestream cigarette smoke challenge in a dynamic test chamber. Proceedings of the 6th International Conference on Indoor Air Quality and Climate, Helsinki, Finland, July 4-8. Submitted.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

13. Musmand JJ, M White, M Lopez, B Mosimann, MA Kaliner and SB Lehrer. Sidestream cigarette smoke induced perturbations of neuropeptides in the respiratory tract of asthmatics. In prep.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Indoor Aldehydes and Bronchial Hyperreactivity

PI: George D. Leikauf, Ph.D.
University of Cincinnati Medical Center
Department of Environmental Health

The researchers will determine if formaldehyde depresses or inactivates mechanisms by which it induces airway hyperreactivity. The airways are at risk from indoor formaldehyde exposure due to the high aqueous solubility and irritant properties of this compound.

Contract No.	90-010	90-010A	90-010B
Contract Execution Date	3/2/90	3/1/91	3/1/92
Contract End Date	3/2/91	3/1/92	3/1/93
No Cost Extension			4/30/93
Budget	$184,370	$164,388	$176,901
Budget Amendment			
Five month report due	NA	8/1/91	8/1/92
Five month report rec	NA	8/19/91	6/92, 9/29/92
Site visit (anticipated)			
Site visit (conducted)	12/19/90		8/10/92
Ten month report due	1/2/91	1/1/92	
Ten month report rec	1/31/91	1/27/92	
Continuation approved			

STATUS: August 1991

Examination of the influence of epithelial derived mediators on airway smooth muscle responsiveness and characterization of the effects of formaldehyde on the release of these mediators is progressing well. Following in vivo exposure of guinea pigs to selected concentrations of formaldehyde, measurements were made on 1) in vivo airway resistance, 2) in vivo airway reactivity, and 3) in vitro airway reactivity. Results indicate that total pulmonary resistance (sR_t) measured by whole-body plethysmography was markedly increased, in vivo reactivity increased, and the reactivity of the smooth muscle in vitro increased.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Experiments involving in vitro exposure of isolated trachea followed by tests of smooth muscle responsiveness in vitro are scheduled to begin 9/91. The in vitro exposure of airway epithelial cells in culture followed by smooth muscle responsiveness in vitro will begin in early '92.

In contrast to the demonstrable effects on physiological tests, histological analysis to date has not demonstrated any changes in inflammatory cells infiltration into the lamina propria on the epithelium. Further, no changes in the number of cilia cells/mm epithelium have been observed. Thus, epithelial damage is subtle at these exposure levels. Project is substantially on schedule.

JANUARY, 1992

Having determined that the contractile response of guinea pig tracheal smooth muscle was greater after in vivo formaldehyde exposure, the investigator is now examining the specificity of this response. Previous studies have demonstrated that epithelial damage/removal increases smooth muscle sensitivity to neuropeptides to a greater extent than to histamine or cholinergic agonists. That is why the original proposal involved the study of neurokinin A and substance P. However, since they found a similar response of guinea pig trachea to both substances, and since there are more published tests conducted with substance P, the less expensive of the two, they conducted an initial series of tests with substance P.

The results of this work indicated that formaldehyde exposure produced a lowering in the cumulative dose of substance P necessary to produce half maximal contraction and potentiated the maximal response. Phosphoramidon, an inhibitor of neuropeptidase present in the airway epithelium, produced a response similar to that produced by formaldehyde, suggesting that formaldehyde induced hyperreactivity in part through epthelial damage and loss of neuropeptidase activity. Further studies are planned to examine this possibility.

The in vitro exposure work has been initiated using isolated trachea and cells in culture and exposing them to formaldehyde. This follows upon the improvement of culture methods of guinea pig tracheal epithelial cells and their growth in serum-free medium. The investigator has indicated that the methods used in the in vitro studies are giving good responses. The project is on schedule.

SEPTEMBER, 1992

In the studies exposing guinea pigs to formaldehyde for 2 h or 8 h, specific pulmonary resistance and airway reactivity (to infused acetylcholine) increased with formaldehyde exposure. After 2 h exposures, resistance was increased at concentrations equal to or greater than 10 ppm, whereas after 8 h exposure, resistance was increased at concentrations greater than or equal to 0.3 ppm. Likewise, after 8 h, reactivity was increased at concentrations greater than or equal to 0.3 ppm formaldehyde. No significant histological changes were noted in airway epithelial cells or in inflammatory cells at 0, 1, 3, 24, 48 or 96

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

h after 3.4 ppm exposure for 8 hours. Tracheal rings isolated from animals exposed to 3.4 ppm x 8 h demonstrated increase maximal response (tension generated) to 10 uM acetylcholine or carbachol. Thus, formaldehyde increases airway reactivity at concentrations relevant to indoor environmental exposures and this response can be examined in vitro.

In addition to increasing cholinergic reactivity, formaldehyde exposure increases reactivity to the neuropeptide, substance P. The findings so far suggest that formaldehyde not only increases neuropeptide release but also degrades neutral endopeptidase and thereby increases the amount and half-life of neuropeptides in the airway. Currently, the PI is extending tests to include different doses of formaldehyde and to include kinetic evaluation of neutral endopeptidase.

In collaboration with Ira Richards at the University of South Florida, the PI has begun to analyze the effects of formaldehyde on human airway smooth muscle. Freshly-isolated tissue (obtained from organ donors) was exposed to formaldehyde in vitro for 3 hours. Immediately upon exposure, formaldehyde induces a transient, dose-dependent contraction. The transient character of the response is reminiscent of the transient increase in resistance observed in guinea pigs in vivo. Moreover, formaldehyde also increases cholinergic reactivity of human airway smooth muscle. Future tests will examine responsiveness to substance P and evaluate neutral endopeptidase activity in human airway tissue.

In addition, the examination of transcellular eicosanoid metabolism between human neutrophil and airway epithelial cells is continuing. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Leikauf, G.D.: Formaldehyde and Other Aldehydes. In: Environmental Toxicants: Human Exposures and Their Effects, M. Lippmann (ed.), Van Nostrand Rheinhold, New York, 1992, pp. 299-310.

2. Swiecichowski, A.L., Long, K.J., Miller, M.L. and Leikauf, G.D.: "Formaldehyde-induced Airway Hyperreactivity In Vivo and Ex Vivo in Guinea Pigs," Environ. Res., (submitted).

3. Leikauf, G.D., Swiecichowski, A.L., Rosbolt, J.P. and Richards, I.S.: "Aldehyde-induced Airway Hyperreactivity," (prepared).

4. Leikauf, G.D. and Driscoll, K.: "Cellular Approaches in Respiratory Tract Toxicology," (prepared).

5. Leikauf, G.D.: "Formaldehyde-induced Airway Hyperreactivity," presentation in Spring '92, Sopron, Hungary.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

MARCH, 1993

In the study of bronchoconstrictive effects of formaldehyde in guinea pigs in vivo and with human airway smooth muscle in vitro, formaldehyde exposures in high concentrations produce transient contractions in both experimental systems. Airway reactivity to acetylcholine was examined in guines pigs in vivo and ex vivo and in human airway tissue in vitro. In each system, formaldehyde reduced the dose of acetylcholine that induced contractions or heighten the maximal responses, indicative of airway hyperreactivity. The dose necessary to induce hyperreactivity in vivo was reduced from greater than 10 ppm to less than or equal to 1.0 ppm when exposures were extended from 2 to 8 hours. These findings suggest that formaldehyde can induce effects that last for greater than 24 hours after exposure to concentrations with environmental relevance.

The study with transcellular eicosanoid metabolism is going very well. The PI has obtained preliminary evidence indicating that human airway epithelial cells and human neutrophils produce more leukotriene B_4 when stimulated in co-culture. This finding is likely to help explain how indoor aldehyde exposure can produce inflammation, since leukotriene B_4 is a potent chemoattractant for inflammatory leukocytes. Because inflammation is linked to asthma, this finding will improve the understanding of the role of epithelial injury in airway inflammation. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Leikauf, G.D., Zhao, Q., Zhou, S., and Santrock, J.:"Ozonolysis Products of Membrane Fatty Acids Activate Eicosanoid Metabolism in Human Airway Epithelial Cells," American Journal of Physiology: Lung Cellular and Molecular Physiology, (submitted).

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Formaldehyde-Induced Activation of Airway Epithelial Cells

PI: **George D. Leikauf, Ph.D.**
University of Cincinnati Medical Center
Department of Environmental Health

Following the work on the initial project, this study will further investigate the cellular basis of formaldehyde-induced hyperreactivity in freshly-isolated human airway tissue and epithelial cells in culture. It will be determined whether formaldehyde (1) decreases airway neutral endopeptidase activity and/or alters eicosanoid biosynthesis, (2) increases chemotactic factor release, and (3) increases transcellular eicosanoid metabolism between leukocytes and airway epithelial cells.

Contract No.	93-08		
Contract Exec Date	5/1/93		
Contract End Date	5/1/94		
No Cost Extension			
Budget	$209,438	$204,199	$213,526
Budget Amendment			
Five month report due	10/1/93		
Five month report rec			
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	3/1/94		
Ten month report rec			
Continuation approved			

STATUS: MARCH, 1993

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Mechanisms Involved in Induction of Allergic Inflammation by House Dust Mites

PI: **Richard J. Looney, M.D.**
University of Rochester School of Medicine
Department of Medicine

The hypothesis that the critical event leading to mite induced respiratory allergies is the outgrowth of mite specific T helper lymphocytes secreting cytokines (such as interleukin-4 (IL-4) and interleukin-5 (IL-5) that promote production of mite specific IgE antibodies and induce an influx of eosinophils into respiratory mucosa) will be investigated. Mite specific T helper cells from mite sensitive, atopic patients will be used.

Contract No.	90-33	90-33A	90-33B
Contract Execution Date	12/20/90	12/20/91	12/20/92
Contract End Date	12/20/91	12/20/92	12/20/93
No Cost Extension			
Budget	$95,949	$105,456	$107,809
Budget Amendment			
Five month report due	5/20/91	5/20/92	5/20/93
Five month report rec	6/3/91	6/2/92	
Site visit (anticipated)			
Site visit (conducted)	11/7/91		
Ten month report due	10/20/91	10/20/92	10/20/93
Ten month report rec	11/7/91	11/3/93	
Continuation approved			

STATUS: August 1991

The PI has established most of the techniques for the first year goals and has begun to gather useable data. He has obtained 7 useful (i.e., proliferated well in response to mite antigen compared to control) mite specific T cell clones. Data has been gathered on cytokine production from mite specific T cells, from freshly isolated peripheral blood mononuclear cells, and from peripheral blood mononuclear cells re-stimulated with PHA and PMA (a combination of mitogens that have been used by other

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

investigators to study cytokine production by T cell clones) after 7 days of stimulation with mite or tetanus.

Studies have been undertaken to compare the abilities of dexamethasone (a glucocorticoid) and forskolin (a material that activates adenyl cyclase resulting in elevated cAMP) to regulate the ratio of gamma-IFN to Il-4, using peripheral blood mononuclear cells stimulated with PHA and PMA. Also, modifications of mite antigen have begun by adding positively charged groups to it (cationization). Preliminary studies indicate that these will induce T cell stimulation, but it is uncertain whether these will be more potent than unmodified allergen, or even if they retain their B cell epitopes. Project is on schedule.

JANUARY, 1992

The studies on the characterization of cytokine production by mite-specific T cells have been expanded by establishing an additional 473 T cell clones from 15 different donors. Overall, the results seem to indicate that there will be a significant but modest difference in cytokine profile for mite clones compared to tetanus clones and this difference would be in the expected direction, i.e., the mite specific clones would appear to make more IL4 relative to gamma interferon than the tetanus clones. That the differences seen have not been striking is probably due to the selection of patients with either no or very mild symptoms related to house dust mite sensitivity. Studies will continue with patients with severe disease.

Work on the factors regulating the outgrowth of allergenic T helper cells has been expanded. The PI has found that forskolin, dexamethasone, IL-4 and possibly inhibitors of 5'lipoxygenase are able to modulate interferon production. The studies on bulk cultures will be extended to look at dose response curves.

Manipulation of the immune response to Der F1 by cationizing Der F1 has met with some difficulty. Unfortunately, all of the protein seemed to precipitate at point of origin in the gels. This approach has not been pursued further. Instead, the PI has purchased some B_6D_2 F1 mice. He intends to begin immunizing the animals with mite antigen bound to alum as soon as he has all the components for the mouse IgE ELISA. Project is on schedule.

SEPTEMBER, 1992

Because the differences found between mite- vs tetanus-specific T cell clones obtained from peripheral blood were small, the PI decided to look at cytokine production by T cells from respiratory mucosa. For these studies he obtained nasal polyps from 6 individuals undergoing polypectomy. All of theses donors had positive skin tests to house dust mite allergen as well as perennial rhinitis. Two of these donors had asthma and had aspirin sensitivity, i.e., aspirin precipitated attacks of asthma.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

From 1218 +/- 1633 pg/ml/million cells of gamma-interferon were produced but only 20 +/- 25 pg/ml/million cells of IL-4 were produced. Spontaneous total and mite-specific IgG, IgA, and IgE production by the mononuclear cells from these polyps resulted in a ratio of IgG:IgA:IgE equaling 7:47:1. This ratio is strikingly different than what is seen in serum. Additional studies on polyp and peripheral blood T cell clones showed large amounts of gamma-interferon produced but very little IL-4. Therefore, despite the fact that these patients were skin test positive and had a large number of eosinophils in their polyps, the cytokine profile did not suggest the activation of TH2 cells. It may be that IL-5 is the critical cytokine for inducing inflitration with eosinophils. The PI is now trying to get his samples assayed for IL-5 to see if his polyp patients are similar to intrinsic (non-allergic) asthmatics in a European study. The PI plans to look at tonsilectomy specimens and recently has been given approval to use normal nasal tissue.

The PI has begun collecting reagents for studies on the manipulation of the immune response to mite allergens. Using peptides for the T cell epitopes of tetanus toxoid and diptheria crim, he is planning to look at whether or not these peptides are good inducers of gamma-interferon production by peripheral blood mononuclear cells from immunized donors. If they are, then they may serve as useful adjuvants for inducing a TH1-like response when linked to Der F1.

The data on nasal polyps will be presented at the Otolaryngology meetings in September by an ENT resident in the PI's lab. Project is on schedule.

MARCH, 1993

Work on the characterization of cytokine production by mite-specific T cells has shown that it is imperative for investigators looking for T cell clones to look at cytokine profiles in primary cultures, since it may be that these cytokines produced early in in vitro culture influence the pattern of cytokine profile of the T cells that eventually grow out. The PI's work is the first study that has done this.

Concerning the factors regulating the outgrowth of allergenic helper T cells, the PI could not find evidence to suggest that the inflammation seen in nasal polyps is similar to that seen in allergic reactions, nor was he able to identify any antigen-specific immune response. All of the work would support the model that the cytokine profile of the TH cells might be determined by local factors in tissue. Since the major difference between a non-allergic and allergic inflammation of the tissue is a degranulation of mast cells by allergen-specific IgE in allergic inflammation, it would seem likely that this event should be very important in determining the type of T cell profile that develops in T cells that infiltrate tissue.

The PI has not given up on devising a better way to conduct immunotherapy for allergic disease. However, his results to date indicate that the regulation of cytokine production by T helper cells is much more complicated than he had originally envisioned. If local tissue factors are of paramount importance in determining the cytokine profile of T

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

cells, then simply trying to induce TH-1 type cells with immunization may not be effective. On the other hand, if IgE binding of allergen is the critical local factor that determines the cytokine profile of infiltrating T helper cells, induction of high levels of blocking antibody may be the most important effect of immunotherapy. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Cytokine Profile of Mite-specific T Cells from Skin Test Positive Donors," R.J. Looney, D. Pudiak, S.I. Rosenfeld. Submitted to the Journal of Allergy and Clinical Immunology, September, 1992.

2. "Accumulation of Gamma Interferon Producing TH1 Helper Cells in Nasal Polyps," C.H. Miller, D.R. Pudiak, F. Hatem, R.J. Looney. Presented at the American Academy of Otolaryngic Allergy Annual Meeting, Washington, D.C., September 10, 1992. Submitted to the Journal of Otolaryngology.

2504065433

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

The Regional Deposition of ETS and its Influence on Radon Dosimetry

PI: John J. McAughey
Harwell Laboratory
Oxfordshire, England

In these studies, the deposition of ETS particles in different regions of the respiratory tract, and the effects of ETS on airborne radioactivity levels and degree of attachment will be measured. Results will be combined in a dose assessment of the effects of ETS on radon dosimetry.

Contract No.	90-29	90-29A	
Contract Execution Date	9/10/90	2/25/92	2/25/93
Contract End Date	9/09/91	2/24/93	2/24/94
No Cost Extension	6 months		
Budget	$80,400	$174,700	$81,700
Budget Amendment			
Five month report due	2/91	6/92	7/93
Five month report received	4/91	6/92	
Site visit (anticipated)			
Site visit (conducted)	4/91, 10/91		
Ten month report due	7/91	12/92	final 2/94
Ten month report received	11/91	3/93	
Continuation approved	1/92	3/93	

STATUS: August 1991

Project is about three months behind schedule. PI (J. Pritchard) left Harwell in August. Co-investigator (J. McAughey) is preparing a report to describe project status and personnel changes. As of April, no problems were anticipated regarding recruitment of volunteers for the study. All necessary radiochemical apparati were constructed and exposure system modified to accomodate oro-nasal breathing.

2504065434

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

STATUS: January 1992

Thoron source has been prepared, installed in glove box system, and attached to breathing engine. Exposure system for ETS and thoron, and computer based valving system and software for controlling and logging breathing patterns have been developed. Test atmospheres of ETS and thoron in the exposure facility have been generated and characterized by measurements of CO (10_6 ppm), tar particulate concentration (1 mg/m^3), particle number ($6x10^6$/cc), and nicotine (0.17 mg/m^3). Thoron progeny measurements indicate that thoron concentrations generated in the chamber will be adequate for the inhalation studies. The "unattached" fraction appeared at larger particle size than normally expected. Therefore, modifications to the thoron delivery system are being made to reduce the "unattached" fraction inhaled (ten fold) so that activity will not be deposited in the lung in a different region to that attached to ETS particles. Volunteer recruitment for exposures is complete.

STATUS: September 1992

Progress is satisfactory. One subject has completed all three exposure regimes (varying breathing pattern) followed by measurement of regional deposition. Four subjects have done single runs for one breathing pattern followed by measurement of regional deposition. The average half time observed for TB clearance was 9.2 h. Clearance values measured at Harwell previously by similar techniques for polystyrene particles and mainstream smoke (both of larger diameter than the surrogate ETS) were around 2 h. Increased clearance half times may be due to deposition lower in the terminal bronchioles of the smaller, non-hygroscopic secondary smoke particles.

STATUS: March 1993

Under three breathing patterns (nose, mouth, mouth-shallow, rapid) the deposition fraction differs, and in all cases are significantly greater than that reported by Hiller et al (1984) of 11+4%. The deposition fraction increases from 43% to 69% on switching from mouth to nasal breathing, but decreases to 22% when switching to a shallower more rapid mouth breathing pattern. ETS particulate matter deposits in slightly lower generations of the lung than mainstream smoke as confirmed by measured clearance half times. Results to date combined with known physicochemical differences between ETS and mainstream smoke suggest that extrapolation of exposure and dosimetric data for the two situations is not appropriate.

2504065435

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

McAughey JJ

Publications, Abstracts, and Presentations Supported by CIAR

McAughey JJ, A Black, AC Wells, DA Knight and JN Pritchard. 1993. The fate of nicotine on ageing of ETS in indoor environments. Abstract. To be presented at Indoor Air '93 Conference, Helsinki, Finland, July 4-8.

Strong JC, A Black, JJ McAughey and DA Knight. 1993. Dosimetry of ETS and attached thoron progeny. Abstract. To be presented at Indoor Air '93 Conference, Helsinki, Finland, July 4-8.

Strong JC, DA Knight and A Black. 1993. A novel method for the radio-labelling of the particulate phase of ETS. J Aerosol Sci. Submitted.

2504065436

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Indoor Air Quality and Energy Parameters Tested with Variable-Air-Volume / Bypass Filtration System

PI: Milton Meckler, P.E.
The Meckler Group
Encino, California

The proposed Variable-Air-Volume / Bypass Filtration System (VAV/BPFS) will be tested under controlled conditions to determine whether this concept improves substantially IAQ and energy conservation compared with the conventional VAV systems used in buildings today. Simulation IAQ models will assess the potential use of the BPFS in indoor environments such as offices. Also, the research team proposes to perform a preliminary analysis of the reduction of exposure vs. the cost of operating each of the control systems.

Contract No.	92-05	
Contract Execution Date	1/29/92	
Contract End Date	10/29/92	(Note:9 month contract)
No Cost Extension	5/31/93	
	7/15/93	

Budget	$109,380
Budget Amendment	$120,380 ($11,000 instr. repairs)
	$127,318 ($6,938 additional filter)

Five month report due	6/29/92
Five month report received	6/24/92

Site visit (anticipated)	
Site visit (conducted)	12/15/92

Ten month report due

Ten month report received

Continuation approved

STATUS: JANUARY, 1992

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

SEPTEMBER, 1992

IITRI built and installed the Bypass Filtration System (BPFS) and developed the study experimental design. During the process of fine tuning the chamber, instrumentation replacement and repairs necessitated the request for an additional $11,000 and a project extension through May '92. Subcontractor D. Moschandreas indicated that the project should be back on track for an observation of the system at a November site visit in Chicago.

MARCH, 1993

As originally designed, the work has progressed satisfactorily following the replacement of the collapsed condenser of the chamber. The initial results appeared promising, however, during discussions with the PIs at the site visit it was agreed that the present filter used for testing was effective in removing VOCs but was not efficient in removing particulate matter emitted from cigarette smoke. Since this inefficiency is related to the filter specs and not to the system design, it was decided to obtain a more appropriate filter and to repeat the necessary experiments. Work is progressing well, despite the difficulties with IITRI officially closing down the chamber facilities.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Injury in Gas Exchange Units Due to Low Level Nitrogen Dioxide

PI: Robert R. Mercer, Ph.D.
Duke University Medical Center
Department of Medicine

The researchers will study phenomena involved in the progression of chronic low level exposures to airborne pollutants and will provide techniques for the isolation of specific sites within the lung which are most likely to demonstrate changes at low levels of exposure.

Contract No.	90-22	90-22A	90-22B
Contract Execution Date	6/5/90	7/1/91	7/1/92
Contract End Date	6/5/91	6/30/92	6/30/93
No Cost Extension	to 6/30/91		
Budget	$202,159	$156,889	$162,749
Budget Amendment			
Five month report due	11/5/90	12/91	11/92
Five month report received	12/01/90	1/92	
Site visit (anticipated)			
Site visit (conducted)	5/8/91		
Ten month report due	4/5/91	5/92	final 6/93
Ten month report received	5/30/91	5/92	
Continuation approved	7/1/91	6/92	

STATUS: August 1991

Project is on schedule. PI has developed more sensitive methods to detect injury and repair of connective tissue fibers in the lungs, and has described the dosimetry model for reactive gas uptake in different gas exchange units in the lung.

STATUS: January 1992

Structural modeling for reactive gas dosimetry is complete. The determined reaction parameters for NO_2 uptake in airways and alveolar regions are being used in simulations of NO_2 uptake in rat lungs. The results of rat exposures to 3 ppm NO_2 with 9 ppm spikes demonstrate

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

significant alterations in interstitial and epithelial compartments at this dose. Predicted dose for the individual ventilatory units correlates strongly with response of epithelium and interstitium of the proximal alveolar region in these high dose exposed rats. Statistical analysis of connective tissue elements in alveolar wall and tip of alveolar septa forming alveoli from this high dose exposed group in underway. Serial section of production, reconstruction, and EM morphometry are complete and half complete for 1.5/3.0 ppm NO_2 and 0.1/0.3 ppm NO_2 groups, respectively.

STATUS: September 1992

Progress is very good. Results of NO_2 exposures indicate significant structural heterogeneity of the lungs (airways branching patterns, number and volume of ventilatory units on any specific airway) between animals. This has been put forth as one of the mechanisms producing significant variations observed in injury by inhaled pollutants. In dosimetry studies, predicted NO_2 uptake based on structural modeling of individual ventilatory units is significantly correlated with alveolar epithelial hypertrophy (AEH) at 3.0/9.0 ppm and 0.5/1.5 ppm NO_2. Compared to results from a similar study with ozone, NO_2 is 5 times less toxic in terms of AEH than ozone in the proximal alveolar region and has a more uniform injury pattern in the ventilatory unit. In morphometry studies, acute exposures to nitrogen dioxide results in alveolar septal hypertrophy with no significant alteration in the connective tissue fibers on lung parenchyma. Alveolar macrophage accumulation is correlated with alveolar septal hypertrophy.

STATUS: March 1993

PI is conducting final stages of data analysis and preparation of final report.

2504065440

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Mercer RR

Publications, Abstracts, and Presentations supported by CIAR

1. Mercer RR, S Anjilvel, FJ Miller, and JD Crapo. 1991. Inhomogeneity of ventilatory unit volume and its effects on reactive gas uptake. J Appl Physiol 70(5):2193-2205.

2. Presentation of 1. above at NIH workshop on environmental lung disease, May 1991.

3. Mercer RR and JD Crapo. 1991. Structural changes in elastin fibers following elastase administration in hamsters. J Appl Physiol 72:1473-1479.

4. Mercer RR, GC McCauley, and S Anjilvel. 1991. Cylindrical approximation of biologic structures. In prep for IEEE Trans on BME.

5. Environmental Criteria and Assessment Office, US EPA, Aug 14, 1991. Workshop on Identification of Ventilation Rate and Respiratory Surface Area for Inhalation RfC Methodology. Invited participant.

6. Office of Technology Assessment, US Congress, Sept 30, 1991. Workshop on Noncancer Health Threats to the Lung. Invited participant.

7. Mercer RR, ML Russell and JD Crapo. 1991. Alveolar septal structure in different species. J Appl Physiol. Submitted.

8. Clean Air Scientific Advisory Committee (CASAC), US EPA, Apr 27-28, 1992. Review of the draft National Ambient Air Quality Standards for Nitrogen Oxides. Consultant.

9. Pinkerton KE, RR Mercer, CG Plopper and JD Crapo. 1992. Distribution of injury and microdosimetry of ozone in the ventilatory units of the rat. J Appl Physiol. In press.

10. Mercer RR and JD Crapo. 1992. Three dimensional analysis of lung structure and its application to pulmonary dosimetry models. In: Toxicology of the Lungs, Gardner DE, JD Crapo, and EJ Massaro (eds.), Raven Press. In press.

11. Miller FJ, RR Mercer and JD Crapo. 1992. Modeling of lower respiratory tract structure in animals and man: Dosimetry and clinical implications. Aerosol Sci and Tech. Submitted.

2504065441

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Indoor Biological Agents: Exposures and Responses in Allergy and Asthma

PI: **Mary Kay O'Rourke, Ph.D.**
University of Arizona College of Medicine
Division of Respiratory Sciences

Building on an established population of 800 individuals representing 300 families which have been defined for purposes of studies of indoor air pollution supported by EPA, this study will take indoor air samples for pollens and other allergens and antigens to be identified by immunologic tests and compare them with respiratory symptomatology determined by questionnaire, illness, and respiratory dysfunction.

Contract No.	90-003	90-003A	90-003B	90-003C
Contract Exec Date	1/29/90	1/9/91	1/9/92	1/9/93
Contract End Date	1/29/91	1/9/92	1/9/93	1/9/94
No Cost Extension				
Budget	$148,437	$181,287	$191,021	$161,402
Budget Amendment				
Five month report due	6/29/90	6/9/91	6/9/92	6/9/93
Five month report rec	6/22/90	6/7/91	7/8/92	
Site visit (anticipated)				4/29-30/93
Site visit (conducted)	11/2/90		3/13/92	
Ten month report due	11/29/90	11/9/91	11/9/92	11/9/93
Ten month report rec	11/27/90	12/16/91	12/31/92	
Continuation approved				

STATUS: August 1991

Pollen and mold data collected during the full year of 1988 have been analyzed. The seasonal distribution of samples collected is consistent with those previously published. The study comparing air-conditioned homes versus evaporative-cooled homes is showing that mold values are appreciably higher in the latter during the summer and early fall months. As the cooling season ends, spore concentrations return to similar magnitudes.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

The PI has found and verified the presence of significant numbers of house dust mites in Tucson. Evidence of Blatta (cockroach) is rare. The most common mite species found in samples is Dermatophagoides farinae; although a few specimens of D. pteronyssinus have been found. The investigation has shown all growth stages of the mites. The first batch of antigen samples (ragweed, Bermuda grass, insect, house dust mite and one mold taxon) obtained from both indoor and outdoor air has been sent to the Mayo Clinic for analysis.

Supplemental subject medical history, blood draws and complete skin testing of the 800 allergic subjects of the study are progressing well. Currently, over 400 subjects have been skin tested. The new skin test data are being entered into the data base and blood samples are being selected for IgE analysis to begin this year. Daily diary data already collected are currently being coded and entered into the data base. Overall, all aspects of the project are on schedule.

JANUARY, 1992

New collection and slide counting procedures were developed to meet the requirements by the QA officer, following the move of Jim Quackenboss to the EPA. (A visit to EPA-Las Vegas Dec. 3-5 resulted in a working arrangement between the PI and the EPA exposure analysis team for analysis of the time/activity diary data from the project to their mutual benefit. This expertise will greatly enhance the project without any additional cost.)

Seasonal and diurnal variability of indoor pollen and mold concentrations has been assessed in the field study in the two test houses. Data has been counted through the spring of 1991. The first data batches are currently being entered into the newly developed data bases, using a Dbase IV format.

The PI is preparing a manuscript of house dust mite analysis in Tucson. Results indicated that isolated mattress samples contain the highest concentration of house dust mites. Overall, mattresses and furniture contain fewer mites than floor samples. Numerous floor samples both in the main room and the bedroom contain mite concentrations exceeding 200 mites per gram of house dust.

The first batch of antigen samples has been sent to the Mayo Clinic for analysis with the results being somewhat troubling. Additional work will be performed to sort out the discrepancies.

On the human health investigations, over 500 subjects have been skin tested, 992 blood samples have been drawn, and 755 IgE samples have been processed. An analysis to determine whether time of year of blood draw influences the IgE concentrations found in the blood has been undertaken. Also, the relationship between health status (including skin test reactivity) and symptom reports is being investigated among normals, allergics and bronchial responsives under conditions of increasing pollen concentration using relative risk values. The development of an exposure model for individuals based on the amount of time spent in the home

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

indoors is being facilitated by the above mentioned intereaction with personnel at EPA-Las Vegas. Project is on schedule.

Book Chapters Submitted for Publicaton

1. "The Importance of Environmental Allergens in the Development of Chronic and Allergic Obstructive Lung Diseases," M.K. O'Rourke and M.D. Lebowitz, in Environmental Respiratory Diseases, eds. S.L. Demeter, E. Cordasco, and C. Zenz.

2. "Medical Palynology," M.K. O'Rourke, to Vaughn Bryant, Playnological Laboratory, Texas A & M University, College Station, Texas.

SEPTEMBER, 1992

Regarding the determination of pollen, mold spore and airborne antigen concentrations in and around houses, graphic evidence demonstrates that less pollen is found indoors regardless of the taxon involved. Frequency of indoor pollen concentration varies seasonally in response to outdoor concentrations. This variance may be greater in seasons with moderate temperatures (i.e., early spring and fall). Currently, the PI is performing principle component analysis on these values to determine the importance of seasonality and determine which taxa respond in like fashion. Spore data are being related to fungal colony data to ascertain their relationship. Next, the PI will examine the relationship between mold colonies, spore and health effects.

In the comparative study of air-conditioned and evaporative-cooled homes, mold concentrations during the summer and fall of 1990 have been examined. Mold values are appreciably higher in the evaporatively cooled home during the summer and early fall months. As the cooling season ends, spore concentrations return to similar magnitudes in each home.

Collections of house dust mites in the homes have shown that isolated mattress samples contain the highest concentration of house dust mites. Overall, mattresses and furniture contain fewer mites than floor samples. Numerous floor samples both in the main room and the bedroom contain mite concentrations exceeding 200 mites per gram of house dust. Samples collected during the winter generally have greater mite concentrations actively reproducing (eggs are visible within the bodies of females). Seasonal patterns illustrate the declining mite concentrations in February, March and April. Mite populations increase with cooler use through the fall. Greatest concentrations are found during the winter when temperature and humidity values are most favorable for mite reproduction. Winter has the greatest number of immature mites.

Immuno-assay work on antigen conentrations from indoor and outdoor air for ragweed, Bermuda grass, insect, house dust mite and 1 mold taxon has been fraught with difficulties. Possible problems include something being wrong with the seum for assay, Tucson air being incredibly free of antigen, or the antigen assay system not being adequate for low continuous

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

exposures. Split samples are being shared with other investigators to resolve these difficulties. The PI will also attempt the blot technique which may prove more sensitive than the elution technique for detecting low level continuous indoor exposure.

The PI has begun to develop an exposure model for individuals based on the amount of time spent in the home indoors vs. elsewhere. Aside from the immuno-assay work, the project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Meeting of the American Academy of Allergy and Immunology, March, 1992, Orlando, Florida.

2. Meeting of the Eighth Palynological Congress, September, 1992, Aix en Province, France.

3. Prepared and submitted manuscript on the prevalence of housedust mites in Tucson.

4. Manuscript relating household characteristics to mite concentrations over a 2 year period, in preparation for Medical Entomology.

MARCH, 1993

Data collection on the relationship between indoor and outdoor pollen and mold concentrations for 1990-1991 continued through 1992. These samples are undergoing additional analysis for atmospheric antigen evaluation of Bermuda grass.

In the field study in test houses, the PI has examined mold concentrations during summer and fall of 1990- Dec. 1991. All samples are counted from the first home; 75% of the samples are counted from the second home. All data should be completed shortly, along with temperature and humidity values.

In the human health studies, supplemental subject medical history, blood draws and complete skin testing of the 800 subjects of the study remains underway. The PI is now current in data entry, validation and cleaning of all health and diary data. Work has begun on the peak flow data and its relationship to environmental measurements. Based on these data, the PI is developing an exposure model for individuals based on the amount of time spent in the home indoors vs. elsewhere. The PI has evidence (textbook example) correlating health effects with indoor pollen concentrations. Additionally, the mold data also looks promising. Project is on schedule.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Associated Manuscripts and Abstracts/Presentations

1. Lebowitz, M.D., O'Rourke, M.K., Paoletti, P., Sears, M.R. and Burrows, B. 1993. Airway responsiveness related to skin test reactivity. American Academy of Allergy and Immunology. Chicago, March 1993.

2. O'Rourke, M.K. and Lebowitz, M.D. 1993. The contribution of indoor pollen to total exposure: Four models. American Academy of Allergy and Immunology. Chicago, March 1993.

3. O'Rourke, M.K., Fiorentino, L., Clark, D., Ladd, M., Rogan, S., Carpenter, J., Gray, D., McKinley, L. and Sorensen, E. 1993. Building materials and importance of house dust mite exposure in the Sonoran Desert. Indoor Air '93. Helsinki, July 1993.

4. O'Rourke, M.K., Van de Water, P.K., Hjelmroos, M.K., Bernardo, M.C., Boyer-Pfersdorf, P. and Lebowitz, M.D. 1993. Indoor pollen and mold exposure among residents of an urban arid environment. Indoor Air '93. Helsinki, July 1993.

5. Stetzenbach, L.M., O'Rourke, M.K., Meldrum, J. and Boyer-Pfersdorf, P. 1993. The relationship between mold spores and colony counts as representatives of airborne fungi. Indoor Air '93. Helsinki, July 1993.

6. Stetzenbach, L.M., O'Rourke, M.K., Meldrum, J. and Boyer-Pfersdorf, P. 1993. Fungal colony and spore counts from homes in the southwest. Journal of Applied Microbiology.

7. O'Rourke, M.K., Moore, C.L. and Arlian, L.G. Factors affecting house dust mite prevalence in an arid environment. Medical Entomology.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Does ETS Promote Arteriosclerosis or Act as a Co-Atherogen?

PI: Arthur Penn, Ph.D.
NYU Medical Center
Department of Environmental Medicine

The objective of the proposed study is to determine whether chronic inhalation of ETS leads to accelerated arteriosclerotic plaque development. The researchers will determine if exposure of cockerels to ETS components results in activation of dominant transforming genes.

Contract No.	90-008	90-008A	90-008B
Contract Execution Date	2/26/90	4/1/91	2/28/92
Contract End Date	2/26/91	3/31/92	2/27/93
No Cost Extension	COST EXTENSION TO 12/31/93		$181,213
Budget	$168,186	$182,041	$174,570
Budget Amendment	1) additional $18,358 for smoke generator 2) 12/90 additional $2800 for nicotine analysis		
Five month report due	9/90	7/91	7/92
Five month report received	10/1/90	----	9/92
Site visit (anticipated)			
Site visit (conducted)	6/26/90		
Ten month report due	3/91	1/92	3/93
Ten month report received	2/18/91	1/92	1/93
Continuation approved	4/11/91	1/92	1/93

STATUS: August 1991

Project is progressing on schedule. PI has completed 60 day sidestream smoke (SS) inhalation study (TPM = 8 mg/m^3) with cockerels. Microanalysis of plaque formations was completed last month. Cockerels pre-treated with DMBA or DMSO and exposed to SS showed no significant differences in degree and size of plaques compared to pre-treated controls. PI is planning a 90-day, 6 hr/day exposure of cockerels to the same TPM level SS as above.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

STATUS: January 1992

The experiment - Six exposure groups, including air controls were given a single injection or five bi-weekly injections of DMBA (PAH carcinogen) or DMSO (solvent), and exposed to sidestream smoke (RSP = 9 mg/m^3) for 2 hr/day from 24-36 weeks of age. None of the treatments had any effect on body weights. None of the treatments had any effect on serum cholesterol levels. The percentage range of aortic segments in each group having measurable plaque compared favorably with values for spontaneous plaques in birds of this age. Relative plaque intensities (RPIs) were not high in any of the groups (15-39%) and none of the treatments were effective at eliciting increases in RPIs. These results indicate that exposure to sidestream smoke under the stated conditions does not play a major role in the intermediate stage of plaque development in this model.
To test the effect in early stages of plaque development, cockerels are being exposed to the same level of SS from 8-24 weeks of age for 6 hr/day, 5 days/wk. 30 animals are in the SS exposure groups and 15 in the air controls.

STATUS: September 1992

Sub-chronic inhalation study is complete. Plaque incidence was not affected by the exposures. Plaque size was significantly increased in the SS-exposed animals.

PI will submit a 1 year non-competitive continuation application at the end of this year to perform the sub-chronic inhalation study at a relevant, typical ETS level found indoors (about one order of magnitude lower TSP than the original study.)

STATUS: March 1993

PI will determine plaque indices for cockerels exposed 6 hr/day, 5 days/wk, 16 weeks (6-22 weeks of age) to two levels of SS - 1200 and 600 ug/m^3 RSP, as part of an intensive dose-response study of daily 6 hr exposures. Work is underway on the 1200 ug/m^3 RSP exposure level.

2504065448

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Penn A

Publications, Abstracts, and Presentations supported by CIAR

1. Penn A and CA Snyder. 1992. Inhalation of sidestream cigarette smoke accelerates development of arteriosclerotic plaques. Science. Submitted. Presented at 1993 annual meeting of the Society of Toxicology, March.

2504060449

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Effects of ETS on Prenatal and Perinatal Lung Development

PI: Kent E. Pinkerton, Ph.D.
University of California, Davis
Department of Veterinary Anatomy

The investigators will determine whether or not exposure to ETS adversely effects lung development in rats. The three major phases of lung development through embryogenesis to the attainment of a mature lung by three or four months of age will be assessed.

Contract No.	90-006	90-006A	90-006B
Contract Execution Date	2/23/90	1/1/91	1/22/92
Contract End Date	2/23/91	12/31/91	12/31/92
No Cost Extension	start date after ETS wkshp 5/1/91		3/31/93
Budget	$200,859	$164,539	$171,261
Budget Amendment		$5,320 carryover of equip funds from year 1	
Five month report due		5/91	5/92
Five month report received		5/91 (SV)	6/92
Site visit (anticipated)			
Site visit (conducted)	7/16/90, 11/5/90, 5/20/91		
Ten month report due	11/90	10/91	final 4/93
Ten month report received	10/24/90	12/91	1/93
Continuation approved	1/1/91	12/91	new 4/1/93

STATUS: August 1991

Project is on schedule and progressing well. 100-day exposure of rats, age birth to 100 days, to sidestream smoke will be completed 9/12/91. At day 7, 14, 21, 50, and 100, cellular kinetics, DNA incorporation, immunocytochemistry, and lung and liver P-450 levels are investigated. Results through day 50 show no body or lung weight differences between exposed and controls. A four-fold induction of P-450 was observed in 50 day old exposed rats. Investigators have been successful in measuring plasma nicotine metabolites to get an estimate of dose to the animals.

2504065450

Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

STATUS: January 1992

Improvements to SS smoke generation system - A cigarette handling and lighting device was constructed to automatically load, light, and smoke 1R4F cigarettes using FTC mainstream conditions. A second smoking system was installed to be used simultaneously with the first but with each's smoking cycle staggered to promote greater consistency of exposure concentrations.
Biomarkers of exposure - Animals housed in wire cages or in open-top plastic cages with wood chip bedding material were simultaneously exposed to SS for 6 and 12 hours. No differences in blood cotinine levels for animals housed under either condition were found. With progressive exposure to SS, plasma nicotine levels averaged 10 ng/ml regardless of exposure length. Maximal plasma cotinine levels (100 ng/ml) were attained after 3 to 5 days of intermittent exposure to SS.
Results of measurement of the relative activity of isozymes 1A1 and 2B in rat lungs indicate that SS has a marked effect on developmental expression of CP450 in the postnatal lung. CP450 1A1 is significantly augmented in neonatal rat lungs from 7 to 21 days of age by exposure to SS and continued exposure to 100 days is associated with persistent elevation.

STATUS: September 1992

Progress is consistently very good.
In utero exposures to ETS - Exposure conditions: Pregnant SD rats from gestational days 2-21 exposed; 6 hours/day, 5 days/wk; RSP (1 mg/m^3), nicotine (350 ug/m^3), CO (6 ppm); gestational days 18 and 21 and postnatal day 1 examined. Significant decreases were noted in body weight at gestation day 21 and postnatal day 1. The cell labelling index for fetal airways demonstrated an age-dependent decrease, but no alteration due to ETS exposure. The labelling index of parenchymal cells had a significant ETS effect at gestational day 18.
Postnatal exposures to ETS - rat pups exposed postnatal days 2-100; examined at 7, 14, 21, 50, and 100 days. Exposure to SS was associated with a significant elevation in isozyme IA1 activity at each time up to 3 times higher than controls. Isozyme IIB activity was unchanged from controls.
Effects of acute vs chronic ETS exposure on cytochrome P450 isozyme activity - Alterations in IA1 and IIB activity occur quickly with exposure to SS (IA1 increases, IIB decreases). Lungs are unable to adapt to long term exposure by returning enzyme activity levels to control levels. A significant depression of isozyme IIB activity was observed in female rats but not in male rats for chronic exposures.

STATUS: March 1993

Progress is good. Project is on schedule. Awaiting final report.

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Publications, Abstracts, and Presentations supported by CIAR

1. Teague SV, K Pinkerton, RA Jenkins, and JH Moneyhun. 1991. ETS exposure system for whole body and nose only exposure of rodents. 1991 American Conference of Governmental and Industrial Hygienists, American Industrial Hygiene Association, Salt Lake City, UT, 18-24 May, p 6.

2. Cardoso WV, L Edwards, KE Pinkerton, CM Ji, R Philpot, CG Plopper. 1991. Immunocytochemical detection of cytochrome P-450 monooxygenases in the neonatal rat lung. Am Rev Resp Dis 143:A92.

Gebremichael A, D Morin, A Chang, S Teague, CG Plopper, AR Buckpitt, KE Pinkerton. 1992. ETS, lung development, and cytochrome P-450 activity in the neonatal rat. Abstract submitted to the 1992 American Thoracic Society Meeting.

Gebremichael A, CG Plopper, AR Buckpitt, KE Pinkerton. 1993. Development of pulmonary cytochrome P450 isoenzymes: Protein expression, activity and response to ETS in postnatal rats. Abstract. Society of Toxicology 1993 Annual Meeting.

Bric JM, KE Pinkerton and JP Joad. 1993. Chronic sidestream smoke effects on airway and pulmonary artery reactivity to serotonin in developing rats. Abstract. American Academy of Allergy and Immunology 1993 Annual Meeting.

In preparation:

2. Cardosa WV, KE Pinkerton, C Ji, RM Philpot, WM Thurlbeck and CG Plopper. Developmental expression of cytochrome P-450 monooxygenase system in rat airways.

3. Cardosa WV, L Stewart, KE Pinkerton, C Ji, GER Hook, G Singh, SL Katyal, WM Thurlbeck and CG Plopper. Comparison of clara cell secretory product expression during bronchiolar epithelial differentiation in the rabbit and rat.

4. Teague SV, KE Pinkerton, RA Jenkins and JH Moneyhun. A sidestream tobacco smoke generation and exposure system for ETS studies. To be submitted to Inhalation Toxicology.

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Effects of Indoor Air Contaminants on Prenatal and Perinatal Lung Development

PI: Kent E. Pinkerton, Ph.D.
University of California, Davis

The investigators will determine dose response effects of in utero and postnatal exposure to ETS on prenatal and perinatal lungs for cell kinetics and tissue characteristics of the developing airways and parenchyma, the levels of cytochrome P450 isozyme activity in the lungs and liver, the distribution of cytochrome P450 isozymes localized immunocytochemically in the lungs, and the cytodifferentiation of nonciliated bronchiolar epithelial (Clara) cells and alveolar type II cells. These studies will serve as critical biomarkers of the sensitivity and specificity of developing lungs to ETS at relevant indoor exposure levels.

Contract No.	93-09		
Contract Execution Date	4/1/93		
Contract End Date	3/31/94		
No Cost Extension			
Budget	$221,843	$189,470	$198,884
Budget Amendment			
Five month report due	8/93		
Five month report received			
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	1/94		
Ten month report received			
Continuation approved			

STATUS: March 1993

Contract fully executed 3/26/93.

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Pulmonary Reactive Uptake of Inhaled Toxic Contaminants

PI: **Edward M. Postlethwait, Ph.D.**
University of Texas Medical Branch
Pulmonary Division

The proposed project is designed to characterize and compare across species (including man) the kinetics of interaction and the predominant substrates involved during the pulmonary airspace absorption of NO_2 and O_3 with the goal of establishing a model for evaluating relative dosimetry. The researchers will delineate the absorption determinants of NO_2 and O_3 within the intact, isolated lung, followed by the determination of the extent to which uptake is localized to within the epithelial lining fluid (ELF).

Contract No.	90-23	90-23A	90-23B
Contract Execution Date	7/1/90	7/1/91 (fax 6/24/91)	7/1/92
Contract End Date	7/1/91	7/1/92	7/1/93
No Cost Extension			
Budget	$126,158	$119,788	$131,306
Budget Amendment			
Five month report due	12/1/90	12/1/91	12/1/92
Five month report rec	1/24/91	12/26/91	12/15/92
Site visit (anticipated)			4/28/93
Site visit (conducted)	3/15/91		
Ten month report due	5/1/91	5/1/92	
Ten month report rec	6/6/91	6/1/92	
Continuation approved			

STATUS: August 1991

Several studies related to nitrogen dioxide reactive uptake by the pulmonary airspace surface were completed. A comparison between bulk phase exposures and "thin films" has been undertaken both for determining mechanisms of toxicity and to further validate the use of isolated epithelial lining fluid (ELF) as an investigational model. The data support the concept that NO_2 reactive absorption is limited to near the

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gas/liquid interface. The kinetic evaluations of the exposed cellular membranes are still in the initial stages.

Data from another series of studies imply that the primary substrates involved in NO_2 reactive absorption are of small molecular weight (less than 1000). Consequently, the PI has begun to explore the relative reactivity of small molecular weight solutes which occur in meaningful concentrations within the ELF. Steady-state exposures of both single and mixed substrates will be studied to determine whether the overall rate of NO_2 absorption is accurately predicted by the first order expression.

The PI has developed a new isolated lung preparation which utilizes a closed exposure system in addition to subatmospheric ventilation. Reactive uptake of nitrogen dioxide within rebreathing lungs is a first order process and displays rate saturation similar to isolated ELF. Also, studies have begun in isolated lungs investigating the effects of vascular perfusion, inspired concentration, and temperature on O_3 uptake. The approximately three-fold increased uptake coefficient has necessitated the development of the chilled lung, which should be operational in a couple of weeks.

Comparative animal studies will begin shortly, using bronchoalveolar lavage (BAL) from rabbits and mice , followed by dogs and sheep. Project is on schedule.

JANUARY, 1992

Work on the further characterization of NO_2 reactive absorption in both intact, ventilating lungs and in isolated, aqueous biological systems has continued. Results indicate that NO_2 absorption is localized to near-surface sites and that the kinetic absorption characteristics of intact lungs and isolated aqueous systems are similar, validating the design of correlating relative dosimetry in freshly harvested epithelial lining fluid (ELF). A recent study has demonstrated that alteration of airspace surface reactants profoundly affects NO_2 absorption by the intact lung. This is the first clear example that composition of airspace reactant pools directly alters dosimetry of an inhaled reactive toxicant. Preparations are being made to perform the multispecies comparative study of NO_2 reactive absorption by airspace surface fluids.

The PI has initiated studies into the mechanisms of O_3 absorption by the pulmonary epithelium and by isolated pulmonary epithelial lining fluid (ELF) and found that O_3 uptake is also mediated via a reaction-dependent component. Methodologies and approaches will follow the NO_2 reactive dosimetry work. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Postlethwait, E. M., Langford, S. D., and Bidani, A. Transfer of NO_2 through pulmonary epithelial lining fluid. Toxicol. Appl. Pharmacol. 109:464-471, 1991.

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2. Postlethwait, E. M., Langford, S. D., and Bidani, A. Interfacial transfer kinetics of NO_2 into pulmonary epithelial lining fluid. J. Appl. Physiol. 71(4):1502-1510, 1991.

3. Postlethwait, E. M., Langford, S. D., and Bidani, A. Kinetics of airspace interfacial transfer of inhaled NO_2 in rebreathing isolated lungs. J. Appl. Physiol. In preparation.

4. Postlethwait, E. M. and Bidani, A. Determinants of inhaled NO_2 transfer across the pulmonary airspace interface. Presented abstract to a NHLBI/NIEHS workshop on "Environmental Lung Disease," Rockville, MD, May 29-30, 1991. (A published proceeding is expected.)

5. Postlethwait, E. M., Langford, S. D., and Bidani, A. Kinetics of NO_2 interfacial transfer into pulmonary epithelial lining fluid. (Abstract) Toxicologist 11(1):106, 1991. (Presented at the Society of Toxicology meeting, Dallas, TX, Feb., 1991.)

6. Postlethwait, E. M., Langford, S. D., and Bidani, A. Penetration of NO_2 through "thin films" of pulmonary epithelial lining fluid. (Abstract) Am. Rev. Respir. Disease 143(4):A700, 1991. (Presented at the American Thoracic Society meeting, Anaheim, CA, May, 1991.)

7. Postlethwait, E. M., Langford, S. D., and Bidani, A. Kinetics of NO_2 uptake in rebreathing isolated lungs. (Abstract) Am. Rev. Respir. Disease 143(4):A700, 1991. (Presented at the American Thoracic Society meeting, Anaheim, CA, May, 1991.)

8. Postlethwait, E.M., Langford, S.D., and Bidani, A. Kinetics of NO_2 airspace absorption in isolated rat lungs. Submitted to: J. Appl. Physiol. 12/91

9. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A., Relative NO_2 reactivity of pulmonary epithelial lining fluid reactants. Toxicol. Appl. Pharmacol. In preparation.

10. Postlethwait, E.M., Langford, S.D., and Bidani, A. Ozone reaction-mediated absorption in isolated rat lungs. Amer. Rev. Respir. Dis. In preparation.

11. Postlethwait, E.M., et al. Reaction-dependent O_3 absorption in isolated rat lungs. (Abstract) The Toxicologist. In press.

12. Postlethwait, E.M., et al. Ozone reactive absorption in isolated rat lungs. (Abstract) Amer. Rev. Respir. Dis. In press.

13. Postlethwait, E.M., et al. Ozone reactive absorption in isolated pulmonary epithelial lining fluid. (Abstract) Amer. Rev. Respir. Dis. In press.

14. Postlethwait, E.M., et al. The effect of surfactant release on NO_2 reactive uptake in isolated rat lungs. (Abstract) Amer. Rev. Respir. Dis. In press.

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SEPTEMBER, 1992

In continued progress toward the evaluation of the comparative airspace surface dosimetry of inhaled reactive gases, the PI's most recent efforts have involved completing the initial characterization of ozone uptake under quasi-steady-state exposure conditions. He has also continued his studies on the effects of in situ airspace surface conditions on NO_2 reactive uptake in isolated lungs. This is an important area of investigation since it uniquely demonstrates that situations which potentially alter conditions at the gas/liquid interface (i.e., exercise, prior exposure, existing lung disease) have the capacity to substantially alter airspace surface dosimetry.

The study which characterizes the NO_2 relative reactivity of potential reactants which are found in the epithelial lining fluid has been completed. The results of this study are of interest in terms of the most reacive and prevalent substrates (which also have relevance to other aspects of pulmonary toxicology) and lead the PI to believe that interfacial conditions within the alveolar space relative to the conducting airways may play an important role in determining local dosimetry and in the genesis of the site-specific pathology which occurs with reactive gas exposure. In addition, the PI has initiated the comparative species studies and, as a result, is preparing for the human component of the proposed work. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. Mixed phase reaction kinetics between pulmonary epithelial lining fluid constituents and gas phase NO_2. Toxicol. Appl. Pharmacol. In preparation.

2. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. Inhaled O_3 is cleared from pulmonary airspaces by reactive absorption. Am. Rev. Respir. Dis. In preparation.

3. Postlethwait, E.M., Langford, S.D., and Bidani, A. Reaction-dependent O_3 absorption in isolated rat lungs. The Toxicologist 12(1):231, 1992. (Presented at the Society of Toxicology meeting, Seattle, WA, February, 1992.)

4. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. The effect of surfactant release on NO_2 reactive uptake in isolated rat lungs. Am. Rev. Respir. Dis. 145(4):A98, 1992. (Presented at the American Thoracic Society meeting, Miami, FL, May, 1992.)

5. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. Ozone reactive absorption in isolated rat lungs. Am. Rev. Respir. Dis. 145(4):A98, 1992. (Presented at the American Thoracic Society meeting, Miami, FL, May, 1992.)

6. Postlethwait, E.M., Langford, S.D., and Bidani, A. Ozone reactive

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absorption in isolated pulmonary epithelial lining fluid. Am. Rev. Respir. Dis. 145(4):A97, 1992. (Presented at the American Thoracic Society meeting, Miami, FL, May, 1992.)

7. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. The effects of aqueous interfacial and gas phase reactants on reactive absorption of inhaled pollutant gases. Annual Conference on Biomedical Engineering Research, Houston, TX, March, 1992.

MARCH, 1993

The data suggest that the pulmonary airspace absorption of inhaled NO_2 and O_3 are rate-limited, in part, by chemical reactions between the toxicants and constituents of the surface lining layer. The presence of solute reactants is a critical requirement for rapid absorption since in the absence of solute reactants, gas phase disappearance rates are relatively insignificant.

NO_2 interfacial transfer follows fixed-order kinetics (first-order) under specified conditions where the initial gas phase concentrations are less than 10 ppm. As such, NO_2 uptake can be mathematically described and extrapolated down to very low (environmentally relevant) concentrations where inspired concentrations by isolated lungs function as a surrogate for tracheal concentrations.

Isolated lung studies have proved extremely valuable for delineating the specific effects of individual parameters which influence the inspired dose rate (i.e., inspired concentrations of O_3 and NO_2, tidal volume (V_t), and ventilation frequency (f)). In addition, the effects of airspace surface area (altered via functional residual capacity (FRC) volumes) have also been determined. Results suggest that, under fixed conditions of inspired concentration, f, and FRC, uptake of both NO_2 and O_3 is linearly related to V_t.

There are clear species-specific differences in NO_2 reactive absorption rates by isolated ELF. The NO_2 effective rate constants (for gas phase removal) display a rank-order which is similar to the rank-order for oxidant susceptibility suggested by other authors. Direct correlation between species-specific, toxicant-specific reactive absorption rates and tissue damage/susceptibility remains to be demonstrated. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Postlethwait, E.M., Langford, S.D., and Bidani, A. 1992. Kinetics of NO_2 air space absorption in isolated rat lungs. J. Appl. Physiol. 73(5):1939-1945.

2. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. 1992. Reactive absorption mediates the intrapulmonary gas phase clearance of inhaled O_3. Am. J. Respir. Cell Mol. Biol. Submitted.

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3. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. 1992. Mixed-phase reaction kinetics of gas phase NO_2 absorption by pulmonary epithelial lining fluid constituents. Tox. Appl. Pharmacol. In preparation.

4. Jacobson, L.M., and Postlethwait, E.M. 1992. Multispecies comparison of NO_2 reactive uptake by pulmonary epithelial lining fluid. Gulf Coast Society of Toxicology, Annual Meeting. ABSTRACT.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

Metabolic Epidemiology of Nicotine Exposure in Nonsmokers
PI: John P. Richie, Jr., Ph.D.
American Health Foundation

The researchers will develop and validate immunochemical methods for the determination of nicotine metabolites including nicotine, cotinine, and trans 3'-hydroxycotinine to enable the conduct of large scale and relevant epidemiological studies in ETS exposure and uptake.

Contract No.	90-21	90-21A	90-21B
Contract Execution Date	6/4/90	12/26/91	
Contract End Date	6/4/91	12/25/92	
No Cost Extension	6 mos.		
Budget	$109,012	$108,212	$ 69,448
Budget Amendment			
Five month report due	12/90	5/92	5/93
Five month report received	2/91		
Site visit (anticipated)			
Site visit (conducted)	2/14/91	1/7/92	
Ten month report due	4/91	10/92	FINAL 12/93
Ten month report received	9/91	9/92	
Continuation approved	9/91	9/92	

STATUS: August 1991

Project is about 4 months behind schedule, but is progressing well at this point. PI is only 10% committed at American Health Foundation now and project underwent some slippage during the transition. CIAR has experienced administrative problems with AHF business office (i.e., CIAR has not received any invoices to date) which presently are being ameliorated. Per co-investigator J. Ritchie, a progress report and continuation application is forthcoming within a couple of weeks. Investigators are continuing work on development of polyclonal antibodies specific for nicotine metabolites. Monoclonal antibody was not sensitive enough. They are working on alternative approaches to assays for measuring nicotine metabolites: affinity chromatography to isolate the hydroxycotinine specific antibodies from crossreactive antibodies to cotinine, and HPLC with electrochemical detection to measure metabolites.

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STATUS: January 1992

Further work with monoclonal antibody approach was unsuccessful. From the results of fusions, antibody producing hybridoma cells are obtained, but they are unstable and do not continue to produce. The investigators are developing polyclonal antibodies for 3'-hydroxycotinine in rabbits. While characterizing an existing polyclonal antibody for cotinine, they found a 40% cross reactivity of this antibody with 3'-trans hydroxycotinine. The rabbit antibody recognizes also cotinine and hydroxycotinine conjugates. The investigators have modified an HPLC method developed for plasma nicotine to use dual electrode amperometric detection and have demonstrated its capability to resolve and detect nicotine, cotinine, and hydroxycotinine in urine.

STATUS: September 1992

Progress is satisfactory. Monoclonal antibodies approach was terminated. The investigators designed a new ELISA which quantifies hydroxycotinine in urine at 5 ng/mL. HPLC assay with amperometric detection was terminated because sensitivity for nicotine metabolites in urine from passively exposed individuals is too low. The investigators demonstrated increased sensitivity for the metabolites with coulometric detection, are defining optimal working conditions for their analysis and that of glucuronide conjugates, and will use this method to validate immunoassay techniques. For initial controlled ETS exposure studies to determine steady state levels of urinary nicotine metabolites after chronic heavy exposure and profile differences among smokers, ex-smokers, and passive smokers, 20 subjects have been recruited and exposed to date.

STATUS: March 1993

PI was contacted for an interim report. Status update pending receipt of the report.

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Source: https://www.industrydocuments.ucsf.edu/docs/xqhl0000

The Structural Basis for Irritant Effects of Indoor Air Pollutants

PI: Herbert S. Rosenkranz, Ph.D.
University of Pittsburgh

The investigators will use a Structure Activity expert system (CASE) to establish the structural basis for the action of sensory irritants occurring in the indoor air environment. Structural determinants for the effect will be determined and compared with those known for other endpoints. Results of this study may make it possible to predict potential activity of untested molecules and yield insight into mechanisms of action.

Contract No.	93-01
Contract Execution Date	1/1/93
Contract End Date	12/31/93
No Cost Extension	

Budget	$73,613
Budget Amendment	

Five month report due	5/93
Five month report received	

Site visit (anticipated)	
Site visit (conducted)	

Ten month report due	10/93
Ten month report received	
Continuation approved	

STATUS: March 1993

Contract fully executed 1/2//93

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Experimental Dosimetry of NO_2 using Short-Lived Radioisotopes

PI: Michael L. Russell, MD
Duke University Medical Center
Department of Medicine

Using oxygen-15-labeled NO_2 as a dosimetry tracer, the investigators will test the hypothesis that a significant alveolar region dose gradient exists causing the proximal region to absorb substantially more NO_2 than the distal region, and that the nasopharynx acts as a major determinate of alveolar NO_2 uptake. Intraspecies comparisons in rats and interspecies comparisons between mice, hamsters, rats, and guinea pigs will be examined for NO_2 deposition differences. The investigation will provide an experimentally-based analysis of NO_2 dosimetry throughout the respiratory tract.

Contract No.	92-01	92-01A	
Contract Execution Date	1/1/92	1/1/93	
Contract End Date	12/31/92	12/31/93	
No Cost Extension			
Budget	$118,713	$122,754	$127,929
Budget Amendment			
Five month report due	5/92	5/92	
Five month report received	9/92		
Site visit (anticipated)	5/93		
Site visit (conducted)			
Ten month report due	11/92	11/93	
Ten month report received	11/92		
Continuation approved	12/92		

STATUS: January 1992

Contract fully executed.

STATUS: September 1992

Project is on schedule. Progress is good.
Tracheal Elution of $N^{15}OO$ - Experiments on the diffusibility of $N^{15}OO$ in the trachea of SD rats demonstrated that the $N^{15}OO$ reaction products elute from the trachea in a bi-exponential manner. Release ratios for

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amounts and half lives of the products suggest that either the reaction products of $N^{15}OO$ are of similar diffusivity but contained in two different physical compartments, or that there are two major categories of reaction products with different diffusivities. To eliminate hematogenous redistribution of reaction products, exposures were performed on freshly killed rats mechanically ventilated via tracheostomy (different tidal volumes). While dosimetry models predict tidal volume effects, no statistically significant differences were observed between the radioactivity retained in each of the different lung lobes. Gas exposure via tracheostomy may have introduced disproportionately more turbulent flow within the trachea at the higher tidal volume and caused more $N^{15}OO$ deposition.

A cryogenic purification system for batch processing $N^{15}OO$ was designed as is currently under construction.

STATUS: March 1993

PI has altered time table as a result of recent findings. Since NO_2 products undergo rapid hematogenous redistribution, the measured tracer distribution from a live animal exposure is different from the actual uptake distribution. Interspecies comparison of nasopharyngeal scrubbing efficiency was delayed until this second year and has been underway for a short time. The ventilatory parameter study is slated for this year rather than the airway/alveolar autoradiography study which will be performed next year. Results of cryogenic purification will appear in upcoming progress report.

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Russell M

Publications, Abstracts, and Presentations supported by CIAR

1. Russell ML, JL Need, RR Mercer, FJ Miller and JD Crapo. 1992. Ventilatory parameter effects on uptake of ^{15}O-labeled NO_2 in rats. Am Rev Resp Dis 145:A92 (Abstract).

2. Miller FJ, JH Overton, JS Kimbell and ML Russell. 1992. Regional respiratory tract absorption of inhaled reactive gases. In: Toxicology of the Lung, Crapo JD, DE Gardner and RO McClellan (eds.). In press.

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Investigations of Ozone Reactive Chemistry in Indoor Environments

P. Barry Ryan, Ph.D.
Harvard School of Public Health

Scope of Work: To develop modeling systems for ozone in indoor environments. The investigators will establish the importance of the contribution of chemical reactivity to human exposures in indoor environments through the use of data on ozone deposition velocities with indoor materials in chamber studies, and evaluation of pollutant concentrations in residences.

Contract No.	90-31	90-31A	90-31B
Contract Execution Date	10/10/90	9/30/91	11/4/92
Contract End Date	10/09/91	9/29/92	11/3/93
No Cost Extension			
Budget	$112,896	$104,118	$111,191
Budget Amendment		$126,627	$124,485
Five month report due	3/91	2/92	3/93
Five month report received	3/13/91	----	
Site visit (anticipated)			
Site visit (conducted)		7/8/92	
Ten month report due	8/91	8/92	final 12/93
Ten month report received	9/91	10/92	
Continuation approved	9/30/91	11/92	

STATUS: August 1991

PI's 10-month report is forthcoming within two weeks per telephone conversation. Project is on schedule. Computer networking among PI's lab, home, and university system has been accomplished. A preliminary compartmental model is running on the Sun workstation. PI is gaining experience in Macintosh system development.

STATUS: January 1992

Ozone deposition studies - Results of trials with latex paint coated glass test sections suggest that painted surfaces are reactive towards ozone. An initial high deposition fraction was observed and suggests that some mechanism involving drying paint or surface saturation controls the ozone

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loss rate. A long-term stable deposition rate suggests another mechanism. The pattern on second exposure is an initial lower deposition (30-40%) followed by a more precipitous decline and leveling off to a value similar to that seen at the end of the first exposure.

STATUS: September 1992

PI has been delinquent in reporting progress over the past year, and had little to add on his progress and results at last site visit in July. He is attempting to submit continuation application by early October.

STATUS: March 1993

Ozone deposition is related to ozone concentration, relative (or absolute) humidity, and the presence of VOCs on surfaces, and simple kinetics determines the complex behavior of ozone on surfaces.

-Changing ozone concentration does not affect the fraction deposited.
-Ozone deposition is linearly associated with relative and aboslute humidity. For paper wallpaper, the effect is less pronounced but still evident.
-Attempts to regenerate surfaces using heptene and styrene were unsuccessful.
-Paper wallpaper displayed no ability, under any experimental conditions, to react with ozone.
-Experiments with vinyl wallpaper showed little effect of relative humidity but surface could be regenerated by heating. This suggests "bake-out" of organic material from interior of wallpaper.
-RH effects dominate latex paint but there is evidence of long-term VOC effect.
-VOC effect dominates vinyl wallpaper deposition.
-Both RH and VOC effects may be operative for paper wallpaper but overall deposition is very low.
-Results of preliminary organic acid experiments on latex paint test sections suggest that the principal secondary acid produced is acetic acid.

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Inflammatory Responses after Indoor Exposure to Airborne Glucan and Endotoxin

PI: Ragnar Rylander, M.D.
University of Gothenburg
Sweden

The investigators will perform an epidemiological study on populations in sick buildings in which the extent of "sick building" symptoms will be evaluated and related to the amount of airborne endotoxin and glucan. Results may explain the origin of symptoms reported and open up a means to control the quality of indoor air.

Contract No.	90-25	90-25A	90-25B
Contract Execution Date	7/9/90	9/2/91	9/2/92
Contract End Date	7/8/91	9/1/92	9/1/93
No Cost Extension	9/1/91		
Budget	$102,756	$145,824	$125,000
Budget Amendment			
Five month report due	12/90	1/92	1/93
Five month report received	3/91	1/92	3/93
Site visit (anticipated)			10/92
Site visit (conducted)	4/91, 10/91, 7/92		
Ten month report due	5/91	6/92	final 9/93
Ten month report received	8/91	8/92	
Continuation approved	8/15/91	yes	

STATUS: August 1991

Project is on schedule. PI continued investigations on association between the extent of symptoms in buildings and amount of airborne glucan and endotoxin. Studies were conducted in office buildings, day care centers, and schools in Sweden. PI has demonstrated an association with glucan in several buildings.

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STATUS: January 1992

Sundsvall school studies data are being analyzed. Harryda (daycare centers) study is ongoing. Dust measurements, questionnaires, and bronchial reactivity measurements are being analyzed. Challenge studies have commenced. To assess experimental design, persons with SBS were exposed to known low levels of glucan, endotoxin or saline in the first study.

STATUS: September 1992

Preliminary conclusions of the Harryda study are that headache and mucus membrane irritation are significantly elevated in buildings where glucan is found compared to control buildings. Dose-response relationships between B-1,3-glucan levels and eye and throat irritation, dry cough, and itching skin were found in four buildings in which these symptoms were prevalent compared to a control building. Results of the first series of laboratory exposure studies demonstrate that exposure to glucan causes an increase in the extent of headache and that endotoxin causes increased stuffy nose symptoms.

STATUS: March 1993

The method to analyze glucan from airborne indoor dust samples is established with continuing cooperation of Japanese scientists.
Data analysis of laboratory challenge experiments comprising measurement of pulmonary function and airway reactivity as well as the registration of symptoms with questionnaires (for 24 subjects) is underway.
Data analysis of field studies comprising these measurements and exposures to airborne endotoxin and glucan in all localities is underway.

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